REMARKS

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-128 and 142-198 were pending in this application before entry of the amendments made herein. Claims 124-126, 169-178 and 192-198 have been withdrawn by the Examiner as being drawn to non-elected inventions. Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168 and 179-191 are currently examined.

Applicant has cancelled claims 124-128, 166, 169-178, 180 and 197 without prejudice to Applicant's right to pursue the subject matter of the cancelled claims in this or other related applications.

Applicant has amended claims 62, 63, 65, 68, 69, 92, 98, 112, 119, 121, 142, 143, 146, 147, 149, 155, 156, 158, 164, 179, 181, 182, 184-186, 188, 192-196 and 198, and added new claims 199-207 for purposes of clarity. In particular, Applicant has amended claims 62 and 193 to recite that the composition comprises an isolated HIV Tat protein which is biologically active, as shown by the ability of said isolated HIV Tat protein, at certain concentrations, to activate virus replication when said isolated HIV Tat protein is added to HIV-1 infected cells, which ability to activate is determined by (A) the rescue of Tat-defective proviruses in HLM-1 cells after the addition of said isolated HIV Tat protein at a concentration of up to 1 μg/ml, or (B) the transactivation of HIV-1 gene expression in cells transfected with HIV-1 promoter-reporter plasmid after the addition of said isolated HIV Tat protein at a concentration of up to 1 μg/ml, and the ability of said HIV Tat protein to do one or both of the following (i) and (ii):

(i) enter and localize in the nuclei of activated endothelial cells or dendritic cells, which entering and localizing is determined by (a) incubating activated endothelial cells or dendritic cells with up to 1 μg/ml of said isolated HIV Tat protein which is labeled with rhodamine, and (b) detecting the presence or absence of rhodamine in the activated endothelial cells or dendritic cells by fluorescence microscopy; or

(ii) activate the proliferation, migration, and invasion of Kaposi's sarcoma (KS) cells or cytokine-activated endothelial cells in culture when said isolated HIV Tat protein is present at a concentration of up to 1 μg/ml.

Claim 146, which depends from claim 62, has been amended to recite that the isolated HIV Tat protein is biologically active, as shown by the ability of said isolated HIV Tat protein to additionally perform (i). New dependent claims 199-207 have been added to recite that the

isolated HIV Tat protein is biologically active, as shown by the ability of said isolated HIV Tat protein to additionally perform (ii). Claim 155 has been amended to be consistent with the language of claim 62 as amended. Support for the amendments can be found in the specification at page 14, line 31 to page 15, line 16.

In addition, Applicant has amended claims 62 and dependent claims 63, 65, 68, 69, 98, 112, 119, 121, 142, 143, 146, 147, 155, 156 and 164 to delete all recitations of "fragments" and "mutants." Claim 193 and its dependent claims 194 and 195 have been amended in a similar fashion.

For purposes of consistency, claim 92 has been amended to replace the term "SEQ ID. No. 2" with "SEQ ID NO:2," claims 149, 158 and 182 have been amended to replace the term "SEQ ID NO. 2" with "SEQ ID NO:2," and claim 192 has been amended to replace the term "SEQ ID NO. 4" with "SEQ ID NO:4."

Claim 179 and its dependent claim 188 has been amended to delete all recitations of "fragments" and "mutants." Claim 179 also has been amended to recite that the isolated HIV Tat protein is a wild type HIV Tat protein. The dependency of claims 181, 182 and 184-186 have been amended to reflect the cancellation of claim 180.

Claim 196 and its dependent claim 198 has been amended to delete all recitations of "fragments" and "mutants." Claim 196 also has been amended to recite that the isolated HIV Tat protein is a wild type HIV Tat protein. The dependency of claim 198 has been amended to reflect the cancellation of claim 197.

No new matter has been added. Upon entry of the present amendments, claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167, 168, 179, 181-196 and 198-207 will be pending in the present application.

I. PRIORITY UNDER 35 U.S.C. § 119

In the Office Action (see page 2, last paragraph), the Examiner acknowledged receipt of the foreign priority document, Italian Patent Application No. RM97A000743 filed December 1, 1997 ("the Priority Application"). However, the Examiner did not mark the relevant sections (*e.g.*, items 12(a)(1)) in the Office Action Summary to reflect acknowledgement of Applicant's claim for foreign priority and receipt of a certified copy of the Priority Application. It is respectfully requested that the Examiner acknowledge Applicant's claim for foreign priority and receipt of the certified copy under 35 U.S.C. § 119 accordingly.

II. INFORMATION DISCLOSURE STATEMENT

On November 17, 2000, Applicant submitted an Information Disclosure Statement ("IDS") with a List of Related Art Cited By Applicant ("List") in the instant application. Upon learning that an Examiner-initialed copy of the List was never returned to Applicant, Applicant's representative telephoned the Examiner on December 13, 2005 regarding this matter. Pursuant to the Examiner's suggestion, Applicant filed in the U.S. Patent and Trademark Office on December 13, 2005 a copy of the IDS and List as filed on November 17, 2000, as well as a copy of the stamped postcard receipt, indicating receipt by the U.S. Patent and Trademark Office of these documents. In the Office Action mailed February 27, 2006, the Examiner indicated that the List was not in compliance with the provisions of 37 C.F.R. §§ 1.97 and 1.98 and MPEP § 609. In response, Applicant submitted on June 14, 2006 a replacement copy of the List ("Replacement List") which properly identified each publication listed by publisher, author, title, relevant pages of the publication, date and place of publication. On May 8, 2008, Applicant resubmitted the Replacement List and again requested that the Replacement List be initialed by the Examiner and returned to Applicant. To date, an Examiner-initialed Replacement List has not been returned to Applicant. Accordingly, Applicant respectfully requests the return of an Examiner-initialed copy of the Replacement List to Applicant.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 62, 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 127, 128, 142-168 and 179-191 are rejected under 35 U.S.C. § 112, first paragraph ("Section 112, first paragraph"), as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that the phrase "wherein said composition is pharmaceutically acceptable for administration to a human" is not supported by the original disclosure or claims as filed, because "[t]he specification of the instant application does not describe a HIV-1 Tat composition that is rid of the toxic HPLC solvents like acetonitrile and trifluoroacetic acid (TFA) and the neurotoxic serine protease inhibitor like phenylmethanesulphonylfluoride or phenylmethylsulfonyl fluoride (PMSF)" (see Office Action, page 3, third paragraph, lines 1-6). The Examiner also alleges that the claims represent a departure from the specification and claims as originally filed, because the specification cites Chang *et al.* (AIDS, 1997 Oct; 11(12):1421-31) ("Chang *et al.*") and

specifically states the inclusion of PMSF in the heparin affinity purification method (see Office Action, page 3, third paragraph, lines 6-9). For the following reasons, Applicant respectfully disagrees.

1. The Legal Standard

To satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d. 1111, 1116 (Fed. Cir. 1991). Compliance with the written description requirement is a question of fact, and the fundamental factual inquiry is whether the specification conveys with reasonably clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. *Id* at 1563-1564; *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, January 5, 2001, pages 1099-1111 ("Written Description Examination Guidelines"), sentence bridging page 1104, right column and page 1105, left column, and page 1105, middle column, second paragraph.

An Applicant can show possession of the claimed invention by describing the claimed invention with all its claimed limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). Possession of the claimed invention may be shown in many ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. *See* Written Description Examination Guidelines, page 1104, right column, fourth paragraph, lines 14-25, and page 1105, right column, last full paragraph. The inquiry into whether the written description requirement is met is a question of fact that must be determined on a case-by-case basis. *Id.* at page 1105, middle column, fifth paragraph, last four lines.

The Written Description Examination Guidelines clearly state that "[t]he absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 U.S.C. 112, ¶ 1, for lack of adequate written description." *See* page 1105,

sentence bridging middle and right columns. In fact, where the level of knowledge and skill in the art is high, information which is well known in the art need not be described in detail in the specification to meet the written description requirement. *See Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (holding that where accessible literature sources provided relevant nucleotide sequence information of a poxvirus genomic region referred to in the claims, satisfaction of the written description requirement does not require recitation or incorporation by reference of the sequences in the specification); *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (holding that when the prior art discloses the sequences for nucleotides, the specification need not reiterate the known sequence information to meet the written description requirement for claimed chimeric genes); *see also* Written Description Examination Guidelines, page 1105, right column, third paragraph, last seven lines.

In particular, *Falkner v. Inglis* is an appeal from a decision by the Board of Patent Appeals and Interferences (BPAI) in an interference concerning an invention directed to a poxvirus vaccine in which an essential gene from the genome of the poxvirus was deleted or inactivated. 448 F.3d at 1360. In *Falkner v. Inglis*, the Court of Appeals for the Federal Circuit (CAFC) affirmed the BPAI's decision that the Inglis application adequately described the invention, even though the Inglis application described poxvirus vectors only in general, with specific examples related instead to herpes viruses, and did not describe which sequences in the viral genome were "essential" or "non-essential." *Id.* at 1366-1368. Specifically, the CAFC set forth the following standards with respect to the written description requirement: "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met...even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Id.* at 1366. Accordingly, the CAFC held that the Inglis applications satisfied the written description requirement even though they did not describe particular poxvirus gene sequences corresponding to the recited "essential" sequences, since one of skill in the art, in view of the state of relevant knowledge at the time of the invention, would know which genes were essential in order to inactivate the genes and practice the invention. *Id.* at 1368. The CAFC in *Falkner vs. Inglis* cited *Capon v. Eshhar*, and stated that "forced reiteration of *known* sequences in patent disclosures would only add unnecessary bulk to the specification." *Id.* (emphasis added). Thus, the case law makes it clear that what is conventional or well known to one of skill in the art need not be disclosed in order to satisfy

the written description requirement. *See Capon v. Eshhar*, 418 F.3d at 1360-1361; *Falkner vs. Inglis*, 448 F.3d at 1368.

In addition, it is well established that the law does not require the claimed subject matter to be described literally (*i.e.*, using the same words) for the disclosure to satisfy the written description requirement; there is no *in haec verba* requirement. *See* Written Description Examination Guidelines, page 1105, left column, second full paragraph, lines 15-19. Case law makes it clear that exacting detail is not necessary to meet the written description requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.

In re Alton, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1583-84 (Fed. Cir. 1996); *see also In re Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q. 795, 796 (C.C.P.A. 1971) ("the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of § 112"). The Court also has held that for purposes of the written description requirement, "examples are not necessary to support the adequacy of a written description." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006).

2. <u>The Specification Provides Sufficient Written Description For The Claims</u>

As a preliminary matter, Applicant submits that claims 127, 128 and 166 have been cancelled, thereby rendering the rejection moot with respect to these claims.

Independent claims 62 and 179 recite the phrase "wherein said composition is pharmaceutically acceptable for administration to a human." Each of claims 63, 65, 66, 68, 69, 89-103, 105-112, 114, 116, 117, 119, 121-123, 142-165, 167 and 168 directly or indirectly depends from claim 62; and each of claims 180-191 directly or indirectly depends from claim 179.

Applicant submits that adequate written description support for the phrase "wherein said composition is pharmaceutically acceptable for administration to a human" can be found in the specification at, for example, page 10, lines 15-16 and 30-31, page 17, lines 17-20, and claim 40 as originally filed[1]. In particular, page 10, lines 15-16 and 30-31 of the specification states that biologically active Tat protein can be for use as a vaccine "to be used in humans"

[1] The specification was amended on June 14, 2006 to recite the subject matter of claim 40 as originally filed.

and "to be administered in humans," respectively, for "prophylactic or therapeutic" purposes; claim 40 as originally filed states that the vaccine further comprises "*pharmaceutically acceptable* carriers and eccipients [sic] to maximize [Tat] activity;" and page 17, lines 17-20 states that "[a]t the moment of use, [Tat] can be resuspended in a *biologically acceptable* fluid" (emphasis added). The specification and claims as originally filed clearly show that the inventor contemplated a composition (*e.g.*, vaccine) comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human. The law does not require the specification to literally describe the claimed subject matter in order to satisfy the written description requirement. *See In re Alton*, 76 F.3d at 1175; *In re Lukach*, 442 F.2d at 969; and Written Description Examination Guidelines, page 1105, left column, second full paragraph, lines 15-19. Thus, a person skilled in the art would, based on the disclosure of the instant application, reasonably conclude that the inventor had possession of the claimed invention.

Regarding the Examiner's allegation that the specification does not describe a HIV-1 Tat composition that is rid of acetonitrile, TFA and PMSF, Applicant submits that methods for modifying the procedures disclosed in the specification so as to avoid acetonitrile, TFA, and PMSF are well known in the art, as evidenced by the Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed May 1, 2007 ("First Magnani Declaration") and the Supplemental Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 filed October 22, 2007 ("Supplemental Magnani Declaration"), and the case law makes it clear that the specification need not describe information which is well known and conventional in the art in order to satisfy the written description requirement. *See Capon v. Eshhar*, 418 F.3d at 1360-1361; *Falkner vs. Inglis*, 448 F.3d at 1368. Instead, the specification only need to describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d at 1563. The specification teaches, contrary to the prejudice in the art, the desirability of administering a biologically active Tat protein to a human (see page 10, lines 4-8 and 12-14; and page 14, lines 16-20). The specification also teaches methods for obtaining a composition comprising biologically active Tat protein, including the methods of Chang *et al.* (see page 25, lines 5-8 and 11-14). In particular, the specification discloses two methods for obtaining a composition comprising biologically active Tat protein: (1) a first method involving high pressure liquid chromatography (HPLC) and ion-exchange chromatography (see specification, page 25, lines 5-8), and (2) a second method involving

heparin affinity chromatography (see specification, page 25, lines 9-26). Neither method yields a Tat composition that is pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179, since the first method would yield a Tat composition tainted with acetonitrile and TFA, and the second method would yield a Tat composition tainted with PMSF, and compositions tainted with these toxic ingredients would not be pharmaceutically acceptable for administration to a human, as discussed in the Second Declaration of Shayne Gad, Ph.D. Under 37 C.F.R. § 1.132 filed June 14, 2006 ("Second Gad Declaration") (see ¶¶5 and 7). However, while the specification does not describe how the Tat compositions could be further processed to remove those toxic ingredients, or how to modify the procedures of Chang *et al.* to avoid the toxic ingredients, the two Magnani declarations show that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, *could* avoid such toxic ingredients without undue experimentation, using information conventional and well known in the art, *once knowledge of the specification had motivated the person skilled in the art to do so*, in order to prepare a composition comprising biologically active Tat protein such that it is pharmaceutically acceptable for administration to a human.

Moreover, to the extent the Examiner is basing the written description rejection on an alleged lack of enablement, Applicant submits that the specification clearly enables the claimed invention, as evidenced, for example, by the First Magnani Declaration and the Supplemental Magnani Declaration. In fact, the Examiner previously raised a lack of enablement rejection in the Office Action mailed November 1, 2006 (see paragraph bridging pages 6-7), but subsequently withdrew the rejection in view of the First Magnani Declaration and the Supplemental Magnani Declaration (see Office Action mailed January 9, 2008, page 4).

Applicant wishes to state for the record that while the two Magnani declarations show that a person skilled in the art *could* avoid the use of acetonitrile, TFA and PMSF, without undue experimentation while obtaining a biologically active Tat protein, neither declaration shows that such a person would have any reason to do so. In fact, the Third Declaration of Barbara Ensoli, M.D., Ph.D. Under 37 C.F.R. § 1.132 filed May 8, 2008 ("Third Ensoli Declaration") is evidence that one of ordinary skill in the art as of December 1, 1997 would not have reason, absent the teachings of the instant application, to modify the known procedures for obtaining a biologically active Tat protein (such as those described in Chang

et al.) in order to obtain a biologically active Tat protein in a composition that would be pharmaceutically acceptable for administration to a human.

For at least the foregoing reasons, Applicant submits that the specification provides sufficient written description for the claimed invention. Withdrawal of the Section 112, first paragraph rejection is respectfully requested.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* (AIDS, 1997 Oct; 11(12):1421-31) in view of Sumner-Smith *et al.* (US 5,646,120), and as evidenced by Gu *et al.* (Sep. Technol., 1994, 4:258-260). Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 127, 128, 142-153, 155-162, 164-168, 179-186 and 189 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Heiman *et al.* (web pages entitled "HIV Vaccines: Where are we Going?" http://www.niaid.nih.gov/daids/vaccine/1998nature.htm), and as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 127, 128, 142-168, 179-187, 190 and 191 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Vogel *et al.* ("A compendium of vaccine adjuvants and excipients." In: Powell MF, Newman MJ, editors. Vaccine design: The Subunit and Adjuvant Approach. Plenum, New York, 1995), and as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Castignolles *et al.* (Vaccine, 1996 Oct; 14(14):1353-60), and as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Ramshaw *et al.* (J. Immunol. Methods, 1977; 18(3-4):251-5), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 127, 128, 142-153, 155-162, 164-168, 179-186 and 188 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Livingston *et al.* (J. Immunol., 1997 Aug 1; 159(3):1383-92), as evidenced by Gu *et al.* Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 127, 128, 142-153,

155-162, 164-168, and 179-186 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chang *et al.* in view of Sumner-Smith *et al.* and Barry *et al.* (Clin. Pharmacokinet., 1997 Mar; 32(3):194-209), as evidenced by Gu *et al.* For the following reasons, Applicant respectfully disagrees.

1. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.*, and As Evidenced By Gu *et al.*

The Examiner alleges that the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made (see Office Action, paragraph bridging pages 9-10). Specifically, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV-1 Tat composition of Chang *et al.* so as to include a further step of treating the purified Tat protein with a pharmaceutically acceptable acid, because Sumner-Smith *et al.* suggests a procedure to exchange the TFA for therapeutic use (see Office Action, page 9, first paragraph, and last paragraph, lines 1-5). The Examiner also alleges that "[t]he skilled artisan would have been motivated to do so to generate a Tat composition acceptable for administration to patients" (see Office Action, page 9, last paragraph, lines 5-7). The Examiner further alleges that "the lyophilization process disclosed by Chang *et al.* necessarily removes the acetonitrile," as evidenced by Gu *et al.*, and that one skilled in the art would have had a reasonable expectation of success since one skilled in the art has been routinely removing acetonitrile by lyophilization (see Office Action, page 8, third paragraph, lines 3-6; and sentence bridging pages 9-10). For the following reasons, Applicant disagrees.

As a preliminary matter, claims 127, 128, 166 and 180 have been cancelled, and thereby rending the rejection moot with respect to these claims. Claims 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 127, 128, 142-153, 155-162 and 164-168 directly or indirectly depend from claim 62, and claims 181-186 directly or indirectly depend from claim 179.

The relevant case law regarding obviousness was discussed in previously filed responses, for example, in the Amendment Under 37 C.F.R. § 1.111 filed May 1, 2007 (see page 18) and the Amendment Under 37 C.F.R. § 1.114 filed May 8, 2008 (see pages 18-19), and is not repeated herein.

As previously discussed in the Response Under 37 C.F.R. § 1.111 with Amendments filed December 13, 2005 (see page 16, last paragraph to page 20, first paragraph), Chang *et*

al. discloses two purification methods: (1) a first purification method involving reversed-phase high pressure liquid chromatography (RP-HPLC) and ion-exchange chromatography (IEC), and (2) a second purification method involving heparin affinity chromatography. As discussed in the Amendment Under 37 C.F.R. § 1.114 filed June 14, 2006 (see pages 18-19), neither method yields a Tat composition that is pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179, because the composition would either contain acetonitrile and TFA (if produced by the first purification method of Chang *et al.*) or PMSF (if produced by the second purification method of Chang *et al.*).

As acknowledged by the Examiner, Chang *et al.* does not expressly teach removing organic solvents such as acetonitrile and TFA at the end of the first purification method to render the Tat composition acceptable for administration to a human (see Office Action, page 8, third paragraph, lines 1-3). Chang *et al.* also does not inherently disclose the removal of acetonitrile and TFA at the end of the first purification method sufficient to render the Tat composition pharmaceutically acceptable for administration to a human. Even assuming *arguendo* that Chang *et al.* removed all acetonitrile by lyophilization (which is not admitted to be the case), there is no reason to believe that all or enough TFA would be removed by the same method sufficient to produce a composition pharmaceutically acceptable for administration to a human. The Second Gad Declaration shows that TFA is not recognized as an allowed pharmaceutical ingredient in any form, and that TFA, as a mutagen and a teratogen, would be strenuously avoided in the production process of any therapeutic (see ¶5, lines 7-9). In fact, the Second Gad Declaration states that compositions of Tat protein purified using acetonitrile and TFA as solvents would not be pharmaceutically acceptable for administration to a human (see ¶5, lines 9-13). Thus, the first purification method of Chang *et al.*, which uses acetonitrile and TFA as solvents and does not teach removal of TFA, does not render obvious a Tat composition which is pharmaceutically acceptable for administration to a human, as recited in claims 62 and 179.

The second purification method of Chang *et al.* also does not teach a Tat composition which is pharmaceutically acceptable for administration to a human. In particular, Chang *et al.* explicitly states that the Tat composition obtained by the second purification method was prepared, washed and eluted with lysis buffer containing PMSF, and thus, included PMSF (see page 1424, paragraph bridging cols. 1 and 2). The presence of PMSF in the Tat composition renders the composition not pharmaceutically acceptable for administration to a human, as evidenced by the Second Gad Declaration (see ¶7).

The above-noted deficiencies are not cured by view of Sumner-Smith *et al.*, or Gu *et al.*, for the further reasons detailed below.

As discussed above, Chang *et al.* is completely silent regarding the removal of TFA from the Tat composition obtained from the first purification method. Thus, even assuming *arguendo* that one of ordinary skill in the art would routinely lyophilize the Tat composition obtained from the first purification method, the Tat composition still would not be pharmaceutically acceptable for administration to a human because some TFA would be expected to still be present in the composition. In the Office Action (see page 9, first paragraph), the Examiner alleges that a peptide purified by HPLC and IEC is typically then treated to exchange TFA with a pharmaceutically acceptable acid, as taught by Sumner-Smith *et al.*, to generate compositions suitable for administration to patients for therapeutic use. However, the Examiner's reason to use the acid exchange reaction of Sumner-Smith *et al.* in order to remove TFA from the Tat composition obtained by the first purification method of Chang *et al.* is based on the alleged desire of one of ordinary skill in the art to administer biologically active Tat protein to a human. This reason, however, cannot stand, since it is contrary to the common understanding at the time of the invention that biologically active Tat protein would be harmful when administered to a human. As previously discussed in the Amendment Under 37 C.F.R. § 1.114 filed May 8, 2008 (see pages 20-23), the Third Ensoli Declaration shows the prejudice in the prior art and clear skepticism and disbelief by experts in the art that taught away from administration of biologically active Tat protein in humans due to the knowledge that biologically active Tat protein had many activities that were believed to result in harmful health effects (see ¶17). Accordingly, one of ordinary skill in the art would have no reason to formulate a composition comprising biologically active HIV Tat protein, such as that disclosed in Chang *et al.*, for administration to humans by removing TFA from the composition with the acid exchange reaction disclosed by Sumner-Smith *et al.* in order to render the composition pharmaceutically acceptable for administration to a human. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, U.S.P.Q.2d 1385, 1396 (2007).

Moreover, use of the acid exchange reaction of Sumner-Smith *et al.* would be expected to destroy the biological activity of the Tat protein; thus its use would fail to give rise to the claimed invention. Sumner-Smith *et al.* discloses transactivation-deficient, HIV TAR-binding compounds which function as antagonists of tat action (see col. 3, lines 49-51), prepared by solid phase synthesis (see col. 7, line 37 to col. 8, line 46), and RP-HPLC

purification using acetonitrile/TFA solvents (see col. 9, lines 44-54). Sumner-Smith *et al.* discloses that the transactivation-deficient compounds have "from about 6 to about 100 or more amide-linked α-amino acid residues" (see col. 3, lines 51-55), but preferably consist of 7 to 12 amino acid residues (see col. 5, line 64 to col. 6, line 20), and the formula R1-(A)m-[X]-(B)n-R2, wherein R1 is H or an N-terminal protecting group; R2 is OH or a carboxyl terminal protecting group; X represents a TAR-binding, transactivation-deficient oligopeptide analogue of the tat basic domain, consisting of from 7 to 12 amide-linked α-amino acid residues; m is 0 or 1; n is 0 or 1; and A and B independent represent one or more amide-linked α-amino acid residues which collectively are selected to retain the transactivation-deficient nature of the compound (see col. 2, lines 44-61; and col. 4, line 49 to col. 5, line 2). In contrast, the Tat protein in the composition of claims 62 and 179 is a biologically active protein, and the acid exchange reaction of Sumner-Smith *et al.* would be expected to destroy the biological activity of the Tat protein purified by RP-HPLC. The Examiner's attention is respectfully directed to the Third Declaration of Mauro Magnani, Ph.D. Under 37 C.F.R. § 1.132 ("Third Magnani Declaration"). Professor Magnani, an expert in the preparation of biologically active Tat protein, states that if the Tat protein is lyophilized after RP-HPLC, and suspended in an aqueous, pH-buffered, neutral solvent, the Tat protein regains its native conformation and biological activity; however, if the biologically active Tat protein and remaining TFA after RP-HPLC elution, lyophilization, and resuspension is exchanged with another acid in an aqueous solvent, such as by being subject to the acid exchange reaction disclosed in Sumner-Smith *et al.* at col. 9, lines 44-62, he would expect the three-dimensional conformation of the Tat protein to be damaged by the acid, which acid is chemically reactive in the aqueous solvent, and thus the Tat protein would be expected to lose biological activity (see ¶8). Thus, exchanging TFA with a pharmaceutically acceptable acid in a composition comprising purified biologically active Tat protein would be expected to destroy the biological activity of the Tat protein in the composition. Accordingly, the combination of the teachings of Sumner-Smith *et al.* and Chang *et al.* fails to establish a *prima facie* case of obviousness.

Regarding Gu *et al.*, Gu *et al.* does not teach or suggest that lyophilization alone would remove the acetonitrile sufficient to produce a composition pharmaceutically acceptable for administration to a human. To the contrary, Gu *et al.* discloses a phase separation method to overcome the problems of equipment demand and energy cost associated with use of lyophilization alone (see page 260, left column, line 3 to right column,

last paragraph). Gu *et al.* discloses removing acetonitrile from RP-HPLC effluent fractions by a phase separation method (see Abstract). In particular, Gu *et al.* discloses that when a RP-HPLC effluent fraction containing 65% (vol.) acetonitrile/35% water/0.1% TFA is stored in a freezer at -17°C for several hours, a phase separation occurs such that a top phase containing 88% (vol.) acetonitrile, and a bottom phase containing 65% (vol.) water and 99%+ of the human growth hormone (hGH) protein, are formed (see Abstract; and page 258, right column, first paragraph). However, the phase separation method of Gu *et al.* is not applicable to removing acetonitrile from compositions comprising biologically active Tat protein. Gu *et al.* indicates that the phase separation "occurs *only* in the [acetonitrile] concentration range of 35-88%" (see page 259, right column, second paragraph, lines 3-4) (emphasis in original), and explains that the reason the hGH protein and its genetically engineered analog (hGHG120R) stay in the bottom phase is probably due to their hydrophilicity (see page 260, sentence bridging left and right columns). As stated in the Third Magnani Declaration, Paragraph No. 5, the Tat protein does not elute at the required acetonitrile concentration range of 35-88% during RP-HPLC, and thus, the phase separation method of Gu *et al.* is not applicable to removing acetonitrile from compositions comprising biologically active Tat protein purified by RP-HPLC, such as the Tat composition obtained by the first purification method of Chang *et al.*

The phase separation method of Gu *et al.* is not applicable to the first purification method of Chang *et al.* for the additional reason that the Tat protein would be expected not to preferentially be present in the bottom, predominantly water, phase, but, rather would be expected to be removed along with the acetonitrile phase or remain at the interface between the water phase and acetonitrile phase (see Third Magnani Declaration, ¶6). The phase separation method of Gu *et al.* is clearly stated to be applicable only to the hGH protein, the genetically engineered hGH analog (hGHG120R), and similar relatively hydrophilic proteins that prefer water to the highly polar acetonitrile solvent (see Gu *et al.*, page 260, sentence bridging left and right columns). As explained in the Third Magnani Declaration, Paragraph No. 6, hydrophilicity profiles computed using ProtScale (http://www.expasy.org/tools/protscale.html), based on the amino acid scale of Hopp and Woods (Proc. Natl. Acad. Sci. U.S.A., June 1981; 78(6):3824-3828), show that the Tat

protein is not relatively hydrophilic like the hGH protein[2] and hGHG120R analog[3], and thus, one of ordinary skill in the art would not expect that biologically active Tat would be preferentially present in the water phase of Gu *et al.*'s phase separation method.

In the Office Action (see page 9, second paragraph, lines 1-2), the Examiner admits that there is no suggestion to avoid the use of PMSF in the second purification method of Chang *et al.* However, the Examiner alleges that "applicant has admitted on the record, as evidenced by the two Magnani declarations...that it is common knowledge and routine experimentation in the art as of 1 December 1997 that a combination of purification steps should decrease levels of endotoxin in the resulting protein preparation and to avoid the use of PMSF in the process by purifying a protein at a pH or a temperature, e.g. near 0°C, that inactivates proteases without harming the protein of interest." (see Office Action, page 9, lines 3-9). Applicant submits that the Examiner has mischaracterized the two Magnani declarations. As previously explained in the Amendment Under 37 C.F.R. § 1.114 filed May 8, 2008 (see page 20), the two Magnani declarations show that a person skilled in the art as of December 1, 1997, based on the teaching of the specification and knowledge common in the art as of December 1, 1997, and using only routine experimentation, would be able to use common knowledge in the art to obtain a composition that was pharmaceutically acceptable for administration to a human, *e.g.*, that lacked PMSF, without undue experimentation once knowledge of the instant specification had motivated him/her to do so. While the two Magnani declarations show that such a person could avoid the use of PMSF, the declarations do not show that it was routine to do so. Neither one of the Magnani declarations states or suggests that the person skilled in the art as of December 1, 1997 would have any reason to modify the known procedures for obtaining a biologically active Tat, which result in a composition that is not pharmaceutically acceptable for administration to humans (see, *e.g.*, Chang *et al.*), to obtain a biologically active Tat in a composition that would be pharmaceutically acceptable for administration to a human. In fact, Applicant submits that

[2] The sequence of the hGH protein used to generate its hydrophilicity profile was the amino acid sequence having GenBank accession number AAA72260, obtained on December 17, 2008 from the online database of the National Center for Biotechnology Information (NCBI) at http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&id=208528, which is 192 amino acids in length or one amino acid residue longer in length than that disclosed in Gu *et al.* at page 258, left column, second paragraph, lines 1-2.

[3] The sequence of the hGHG120R analog used to generate its hydrophilicity profile is the sequence of GenBank accession number AAA72260, except that the glycine (G) residue at position 121 is replaced with arginine (R).

the person skilled in the art as of December 1, 1997 would not have reason to modify the known procedures for obtaining a biologically active Tat (including the procedures disclosed in Chang *et al.*) to obtain a biologically active Tat in a composition that would be pharmaceutically acceptable for administration to a human, in view of the prejudice and skepticism in the art as explained in the Third Ensoli Declaration. The Examiner also has not come forward with any reason to avoid the use of PMSF. Thus, Applicant submits that the Examiner's reliance on the two Magnani declarations is misplaced, and based on improper hindsight. *See KSR*, 127 S. Ct. at 1742.

For the foregoing reasons, Applicant submits that claims 62 and 179 and their dependent claims are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, as evidenced by Gu *et al.* Withdrawal of this Section 103(a) rejection is respectfully requested.

2. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 114, 119, 127, 128, 142-153, 155-162, 164-168, 179-186 and 189 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Heiman *et al.*, and As Evidenced By Gu *et al.*

As discussed above, Chang *et al.* does not teach or suggest a Tat composition that is rid of all ingredients, such as acetonitrile, TFA and PMSF, that would render the composition not pharmaceutically acceptable for administration. The Examiner's reason to use the acid exchange reaction of Sumner-Smith *et al.* in order to remove TFA from the Tat composition obtained by the first purification method of Chang *et al.* is based on the alleged desire of one of ordinary skill in the art to administer biologically active Tat protein to a human, which cannot stand since it directly contravenes the evidence in the Third Ensoli Declaration, which shows the prejudice in the prior art and clear skepticism and disbelief by experts in the art that taught away from administration of biologically active Tat protein in humans due to the knowledge that biologically active Tat protein had many activities that were believed to result in harmful health effects. Moreover, subjecting the Tat compositions of the first purification method of Chang *et al.* to the acid exchange reaction of Sumner-Smith *et al.* is expected to destroy the biological activity of the Tat protein, thus failing to yield a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human (see Third Magnani Declaration, ¶8). The phase separation method of Gu *et al.* is inapplicable to biologically active Tat protein because the Tat protein does not elute at the required acetonitrile concentration range of 35-88% (see Third Magnani Declaration, ¶5); moreover, the Tat protein would be expected not to preferentially be present

in the water phase, but, rather much of the Tat protein would be expected to be removed along with the acetonitrile phase or remain at the interface between the water phase and acetonitrile phase (see Third Magnani Declaration, ¶6). Regarding the Tat composition obtained from the second purification method of Chang *et al.* that is tainted with PMSF and thus not pharmaceutically acceptable for administration to a human, the Examiner has not come forward with any reason for one of ordinary skill in the art to avoid the use of PMSF.

Heiman *et al.* does not cure the deficiencies of any of these references, because Heiman *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Heiman *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Heiman *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

3. Claims 62, 63, 65, 66, 68, 69, 89-97, 101-103, 105-111, 116, 117, 121, 122, 127, 128, 142-168, 179-187, 190 and 191 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Vogel *et al.*, and As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, and as evidenced by Gu *et al.* Vogel *et al.* does not cure the deficiencies of any of these references, because Vogel *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Vogel *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use

the teaching of Vogel *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

4. Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 99, 101-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Castignolles *et al.*, and As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, and as evidenced by Gu *et al.* Castignolles *et al.* does not cure the deficiencies of any of these references, because Castignolles *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Castignolles *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Castignolles *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

5. Claims 62, 63, 65, 66, 68, 69, 89-96, 98, 100-103, 105-109, 111, 127, 128, 142-153, 155-162, 164-168 and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Ramshaw *et al.*, and As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, and as evidenced by Gu *et al.* Ramshaw *et al.* does not cure the deficiencies of any of these references, because Ramshaw *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Ramshaw *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Ramshaw *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

6. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 112, 127, 128, 142-153, 155-162, 164-168, 179-186 and 188 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Livingston *et al.*, and As Evidenced By Gu *et al.*

For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, and as evidenced by Gu *et al.* Livingston *et al.* does not cure the deficiencies of any of these references, because Livingston *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Livingston *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Livingston *et al.* to further modify the Tat composition of Chang *et al.* in

order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

7. Claims 62, 63, 65, 66, 68, 69, 89-96, 101-103, 105-109, 111, 123, 127, 128, 142-153, 155-162, 164-168, and 179-186 Are Not Obvious Over Chang *et al.* In View of Sumner-Smith *et al.* and Barry *et al.*, and As Evidenced By Gu *et al.*

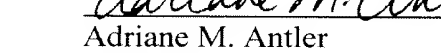
For the reasons discussed above, Applicant submits that claims 62 and 179, as well as their dependent claims, are not obvious over Chang *et al.* in view of Sumner-Smith *et al.*, and as evidenced by Gu *et al.* Barry *et al.* does not cure the deficiencies of any of these references, because Barry *et al.* also does not teach or suggest a composition comprising a biologically active Tat protein that is pharmaceutically acceptable for administration to a human; thus, Barry *et al.* does not provide the missing suggestion. Again, the Examiner relies on an unfounded belief that one of ordinary skill in the art would be motivated to use the teaching of Barry *et al.* to further modify the Tat composition of Chang *et al.* in order to arrive at a Tat composition which is pharmaceutically acceptable for administration to a human. This is contradictory to the evidence presented in the Third Ensoli Declaration that one of ordinary skill in the art would not be motivated to formulate a biologically active Tat into a composition that is pharmaceutically acceptable for administration to a human. Thus, there is no suggestion or motivation or any other reason based on Chang *et al.*, alone or in combination with in any of the other references cited in support of this Section 103(a) rejections, to modify the purification methods of Chang *et al.* so that acetonitrile, TFA and PMSF, that are not pharmaceutically acceptable for administration to a human, are avoided. It is respectfully submitted that this Section 103(a) rejection is in error and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: January 8, 2009



32,605
Adriane M. Antler (Reg. No.)
JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

Enclosures